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ORIGINAL ARTICLE

The effect of repetitive transcranial magnetic stimulation on food choice-related self-control in patients with severe, enduring anorexia nervosa

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Abstract

Objective: Individuals with anorexia nervosa (AN) pursue low-fat, low-calorie diets even when in a state of emaciation. These maladaptive food choices may involve fronto-limbic circuitry associated with cognitive control, habit, and reward. We assessed whether high-frequency repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) influenced food-related choice behavior in patients with severe, enduring (SE)-AN.

Method: Thirty-four females with SE-AN completed a Food Choice Task before and after 20 sessions of real or sham rTMS treatment and at a 4-month follow-up. During the task, participants rated high- and low-fat food items for healthiness and tastiness and then made a series of choices between a neutral-rated food and high- and low-fat foods. Outcomes included the proportion of high-fat and self-controlled choices made. A comparison group of 30 healthy women completed the task at baseline only.

Results: Baseline data were consistent with previous findings: relative to healthy controls, SE-AN participants showed a preference for low-fat foods and exercised self-control on a greater proportion of trials. There was no significant effect of rTMS treatment nor time on food choices related to fat content. However, among SE-AN participants who received real rTMS, there was a decrease in self-controlled food choices at post-treatment, relative to baseline. Specifically, there was an increase in the selection of tasty-unhealthy foods.

Discussion: In SE-AN, rTMS may promote more flexibility in relation to food choice. This may result from neuroplastic changes in the DLPFC and/or in associated brain areas.

KEYWORDS

anorexia nervosa, eating behavior, eating disorders, food choice, repetitive transcranial magnetic stimulation, self-control

Bethan Dalton and Karin Foerde are the co-first authors. Both the authors have contributed equally.

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1 | INTRODUCTION

Anorexia nervosa (AN) is a serious psychiatric disorder involving food restriction and other weight-control behaviors (e.g., excessive exercise and self-induced vomiting), body image disturbance, and a fear of weight gain (American Psychiatric Association, 2013). Treatments are predominantly psychological and/or behavioral therapies (including nutritional interventions), and are moderately effective (Brockmeyer, Friederich, & Schmidt, 2018). Repetitive transcranial magnetic stimulation (rTMS) has been tested as a neuromodulatory treatment for severe, enduring (SE)-AN (Dalton, Bartholdy, Campbell, & Schmidt, 2018; Dalton, Campbell, & Schmidt, 2017) and may be a useful tool for altering self-control mechanisms (Figner et al., 2010).

Maladaptive (excessive) self-control is commonly described in AN, affecting dietary choices, emotion regulation, and the ability to delay gratification, among other processes (Fairburn, Shafran, & Cooper, 1999; Lavender et al., 2015; Steward et al., 2017). Self-control refers to a range of competencies (e.g., impulse/inhibitory control, working memory, and attentional and cognitive flexibility; Hughes, 2011) employed to initiate, maintain, and control thoughts, behaviors, or emotions in the enactment of goal-related behavior (Pandey et al., 2018; Strauman, 2017). It has been proposed that the maladaptive pursuit of low-fat foods and restriction of food intake in AN can be considered excessive self-control (Fairburn et al., 1999). For example, people with AN tend to consume low-fat and low-calorie diets despite being underweight (Baskaran et al., 2017; Hadigan et al., 2000; Mayer, Schebendach, Bodell, Shingleton, & Walsh, 2012; Misra et al., 2006), and this is persistent and contributes to relapse (Mayer et al., 2012; Schebendach et al., 2019).

The Food Choice Task has been shown to capture the restrictive food choices characteristic of AN and to identify associated neural correlates (Foerde, Steinglass, Shohamy, & Walsh, 2015; Steinglass, Foerde, Kostro, Shohamy, & Walsh, 2015). For example, individuals with AN have been reported to show greater functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and the dorsal striatum for low-fat foods than for high-fat foods, whereas healthy control (HC) participants showed the opposite (Foerde et al., 2015). The task has also been used to assess self-control: opportunities for using self-control arise when food items have incongruent ratings of healthiness and tastiness, that is, they are *tasty and unhealthy*, or *non-tasty and healthy*. It is assumed that self-control is then implemented when a healthy, less tasty food item is selected or an unhealthy, tasty food item is *not* selected. Individuals with AN have been reported to exercise self-control on a greater proportion of trials where there is a conflict between healthiness and tastiness ratings, than HCs (Foerde et al., 2015). Specifically, the AN participants tended to choose the healthier food item, regardless of tastiness. More broadly, the task has been used to examine neural processes related to self-control. Hare, Camerer, and Rangel (2009) reported that healthy individuals, when exercising self-control, showed

increased activity in the DLPFC. Recent research has provided further support for the role of the DLPFC in self-control associated with food choice (Chen, He, Han, Zhang, & Gao, 2018; Lopez, Courtney, & Wagner, 2019). Given the involvement of the DLPFC in food choices and reports of its involvement in pathological mechanisms in AN (Compan, Walsh, Kaye, & Geliebter, 2015; Dunlop, Woodside, & Downar, 2016; Frank, Shott, & DeGuzman, 2019), we have investigated how modulating neural activity in this area may influence food choice.

rTMS is a form of non-invasive brain stimulation that uses an electromagnetic field to alter neuronal activity in a target brain area (George & Aston-Jones, 2010). High-frequency rTMS (stimulatory; >10 Hz) to the left DLPFC has been proposed as a promising treatment option for patients with SE-AN (Dalton et al., 2017; Dalton et al., 2018), as it improves eating disorder (ED) and affective symptoms (McClelland, Kekic, Campbell, & Schmidt, 2016; Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013). Furthermore, qualitative feedback from five patients with SE-AN and their carers following 20 sessions of rTMS suggested that some patients felt more able to manage food-related difficulties and had a more relaxed approach to food choice (e.g., trying new foods) after rTMS treatment (McClelland et al., 2016).

The main aim of our study therefore was to assess whether 20 sessions of high-frequency rTMS to the left DLPFC altered food choices (measured using the Food Choice Task) among people with SE-AN. Specifically, we explored whether rTMS treatment influenced food choices, measured by the choice of high-fat foods and self-controlled options.

2 | METHODS

We used a UK-based sample of SE-AN and HC participants to investigate/confirm published data on the use of the Food Choice Task in AN (Foerde et al., 2015; Steinglass et al., 2015). To test the effect of rTMS on food choice, we used data collected as part of a randomized controlled feasibility trial investigating multi-session ($n = 20$) high-frequency rTMS to the left DLPFC as a treatment for SE-AN (Trial registration: ISRCTN14329415). Methodological details have been reported in full in Bartholdy, McClelland, et al. (2015; TIARA study protocol) and Dalton, Bartholdy, McClelland, et al. (2018). The study received ethical approval from the London—City Road and Hampstead Research Ethics Committee (Reference: 15/LO/0196) and the King's College London Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (Reference: HR-15/16-2836).

2.1 | Participants

Thirty-four community-based women (≥ 18 years) with SE-AN were recruited from specialist ED services in London and via online advertisements. Participants were required to have a current Diagnostic

and Statistical Manual of Mental Disorders (DSM)-5 diagnosis of AN (American Psychiatric Association, 2013) with a body mass index (BMI) $>14 \text{ kg/m}^2$, a minimum illness duration of 3 years and have completed at least one National Institute for Health and Care Excellence (NICE; 2017)-recommended specialist psychotherapy or specialist day-patient or inpatient treatment for their ED. Our definition of SE-AN is in line with, albeit somewhat less strict than, recent proposals for characterizing SE-AN (Broomfield, Stedal, Touyz, & Rhodes, 2017; Hay & Touyz, 2018).

HC women ($n = 30$; ≥ 18 years), with a BMI in the healthy range ($20\text{--}25 \text{ kg/m}^2$), were recruited via online and poster advertisements at King's College London to provide a comparison group. Exclusion criteria were current/past psychiatric illness or a family history of an ED. HCs completed the baseline assessment only.

Additional exclusion criteria for all participants related to magnetic resonance imaging (MRI) contraindications (e.g., presence of neurological disease or head trauma) and TMS contraindications (e.g., epilepsy or seizures) for the participants with SE-AN. Participants completed a telephone screening to confirm eligibility. This included the Eating Disorder Diagnostic Scale (Stice, Telch, & Rizvi, 2000) to assess the presence/absence of ED symptoms in the AN and HC groups, respectively, and the researcher version of the Structured Clinical Interview for DSM-IV Axis I Disorders Screening Module (First, Spitzer, Gibbon, & Williams, 2002) to confirm the absence of any psychiatric disorders in the HC participants. All participants provided informed consent.

2.2 | Food Choice Task

Full methodological details of the Food Choice task can be found in Steinglass et al. (2015). The Food Choice Task has been reported to have high test-retest reliability (in HCs; Foerde et al., 2018) and has been validated in patients with AN: caloric intake at lunch significantly correlated with the frequency with which AN participants chose high-fat foods in the task (Foerde et al., 2015).

Briefly, the Food Choice Task is comprised of three phases (Figure 1): the Healthiness Rating phase and Tastiness Rating phase (order of these blocks were counterbalanced), followed by the Food Choice phase. Across all three phases of the Food Choice Task, participants

had 4 seconds per trial to provide their response. During each of these blocks, participants were shown images of the same 76 food items on a computer screen, chosen to be representative of a range of dietary choices. Specifically, 38 food items had a low-fat content and 38 were high-fat (items with $>30\%$ of calories derived from fat; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

In the Healthiness block, participants rated how healthy the food item was on a 5-point scale from "Unhealthy" to "Healthy" and in the Tastiness block, participants rated the tastiness of the food item on a 5-point scale from "Bad" to "Good" (order of rating scales were counter balanced). Following completion of these phases, one food item that had been rated as "Neutral" (a score of 3) for both Healthiness and Tastiness was automatically selected as a neutral reference item to be used in the Choice block. If no item was rated as neutral on both scales, the reference item was selected from those rated "Neutral" on the Healthiness scale and "tasty" on the Tastiness scale, as it would have greater overall value than an unhealthy item for a participant who made decisions based on health information. This followed the same algorithm used previously (Foerde et al., 2015; Steinglass et al., 2015).

In the Choice block, participants indicated their strength of preference for the trial-unique food item, as compared with the neutral-rated reference item. The reference item did not change throughout the Choice block and was visible throughout on the left side of the screen. A rating of 1 or 2 indicated selection of the reference item and a rating of 4 or 5 indicated selection of the trial-unique food item. Participants were instructed to imagine that they would receive a snack-sized portion of one of their selections at the end of the study.

The main outcome on the task was the proportion of high-fat trial-unique food items chosen over the reference item. The secondary outcome was the proportion of self-controlled choices that were made (i.e., choosing healthy, less tasty foods or not choosing unhealthy, tasty foods).

2.3 | Additional measures

The Eating Disorder Examination-Questionnaire (EDE-Q) (Fairburn & Beglin, 2008) assessed ED symptoms and behaviors over the previous 28 days. The Depression Anxiety and Stress Scales—Version 21

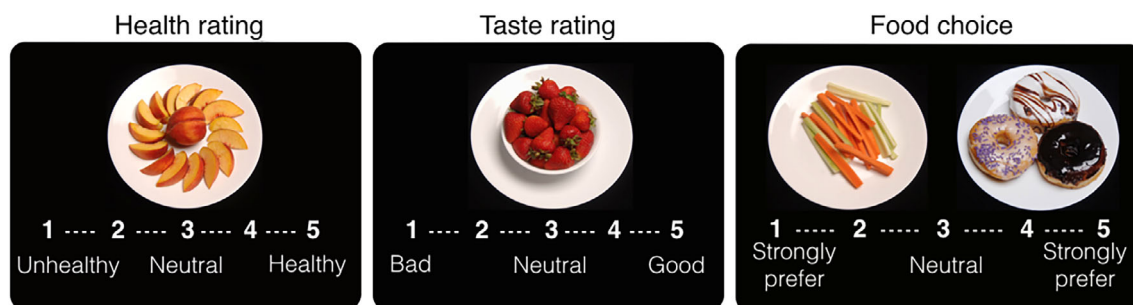


FIGURE 1 Examples of the three blocks of the Food Choice Task [Color figure can be viewed at wileyonlinelibrary.com]

(DASS-21; Lovibond & Lovibond, 1995) measured general psychopathology, including depression, anxiety, and stress, over the previous 7 days. Data from other questionnaires administered are reported in Dalton, Bartholdy, McClelland, et al. (2018).

2.4 | Procedure

2.4.1 | Baseline assessment

Both SE-AN and HC participants attended a research session at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. Participants' height and weight were measured. Following an MRI scan, participants completed the Food Choice Task, along with additional computer tasks and a battery of questionnaires.

2.4.2 | rTMS trial

Following the baseline assessment, the SE-AN participants were randomly allocated to receive 20 sessions (over 4 weeks) of real ($n = 17$) or sham ($n = 17$) neuro-navigated rTMS in addition to treatment-as-usual (e.g., specialist ED outpatient or day-patient treatment, or no current treatment). The Magstim Rapid device and Magstim D70-mm air-cooled real and sham coils were used to administer rTMS. Participants in the real group received 20 sessions of high-frequency (10 Hz) rTMS at 110% of their individual motor threshold, consisting of twenty 5-second trains with 55-second inter-train intervals delivered to the left DLPFC (a total of 1,000 pulses delivered over each 20-minute session). Sham stimulation was administered at the same parameters using a sham coil.

Participants repeated the baseline assessment within 1 week of completing rTMS treatment (post-treatment; 1-month post-randomization) and at a follow-up (4-months post-randomization; without the neuroimaging component) prior to unblinding ($n = 30$; $n = 16$ real rTMS, $n = 14$ sham rTMS).

2.5 | Statistical analysis

Demographic characteristics were compared between diagnostic groups (HC vs. SE-AN) and rTMS treatment groups (real vs. sham rTMS) at each assessment time point: baseline, post-treatment, and follow-up) using unpaired t tests. Tests were two-tailed unless otherwise specified. If unequal variances were indicated, degrees of freedom were adjusted accordingly. Between-group effect sizes (Cohen's d with 95% confidence intervals) for clinical outcomes at post-treatment and follow-up (adjusted for baseline) were calculated.

Food Choice Task data were analyzed using multilevel regression models (lme4 linear mixed effects package for R; Bates, Maechler, & Bolker, 2012) in order to account for random effects, unbalanced data, and to minimize the influence of outliers. In all analyses, models included by-subject random intercepts and slopes (Barr, 2013).

Continuous outcome rating data from the Healthiness and Tastiness phases were modeled using multilevel linear regression. When entered as independent variables, continuous rating data were z -scored. The significance of the partial correlation coefficients was assessed by χ^2 statistics and accompanying p values derived for the estimates from Type-III analysis of variance tables from the ANOVA function in the car package for R (Fox et al., 2012).

For Choice phase data, choices on the five-point scale were converted to binary "Yes" or "No" preferences for the trial-unique food item versus the reference item: responses of 1 or 2 on the Likert scale were converted to "No" (0) and responses of 4 or 5 were converted to "Yes" (1); neutral responses of 3 were omitted from analyses. Binomial choice data were modeled with multilevel logistic regression, in which participant choice (selection of the trial-unique food item over the reference food) was the dependent variable.

For analyses of "self-control" in the Choice phase, trials were first categorized as to whether they presented an opportunity for self-control or not, and the proportion of such trials was calculated. Self-control opportunities arose on trials with incongruent Healthiness and Tastiness ratings (see Figure 3A): food items rated tasty *and* unhealthy or non-tasty *and* healthy. On such trials, self-control was assumed to be implemented if a tasty and unhealthy item was *not* chosen (i.e., the

TABLE 1 Demographic and clinical characteristics for the healthy control and anorexia nervosa participants at the baseline assessment

	Healthy controls ($n = 29$)	Anorexia nervosa ($n = 30$)	Group comparison
Age (years) (median [IQR])	25.00 (5.00)	27.00 (11.50)	$U = 331, p = .115$
Illness duration (years) (mean \pm SD)		15.70 \pm 11.60	
AN-R/AN-BP (n)		21/9	
BMI (kg/m^2) (mean \pm SD)	21.80 \pm 1.50	15.90 \pm 1.40	$t(56) = 15.2, p < .001$
EDE-Q Global (median [IQR])	0.27 (0.56)	4.28 (1.53)	$U = 1, p < .001$
DASS-21 Depression (median [IQR])	2.00 (2.00)	28.00 (16.00)	$U = 9.5, p < .001$
DASS-21 Anxiety (median [IQR])	2.00 (2.00)	14.00 (16.00)	$U = 60, p < .001$

Note: BMI, EDE-Q, and DASS-21 data were missing from one participant with AN.

Abbreviations: AN-BP, anorexia nervosa binge-eating/purging type; AN-R, anorexia nervosa restricting type; BMI, body mass index; DASS-21, Depression Anxiety and Stress Scales—Version 21; EDE-Q, Eating Disorder Examination Questionnaire; IQR, interquartile range; SD, standard deviation.

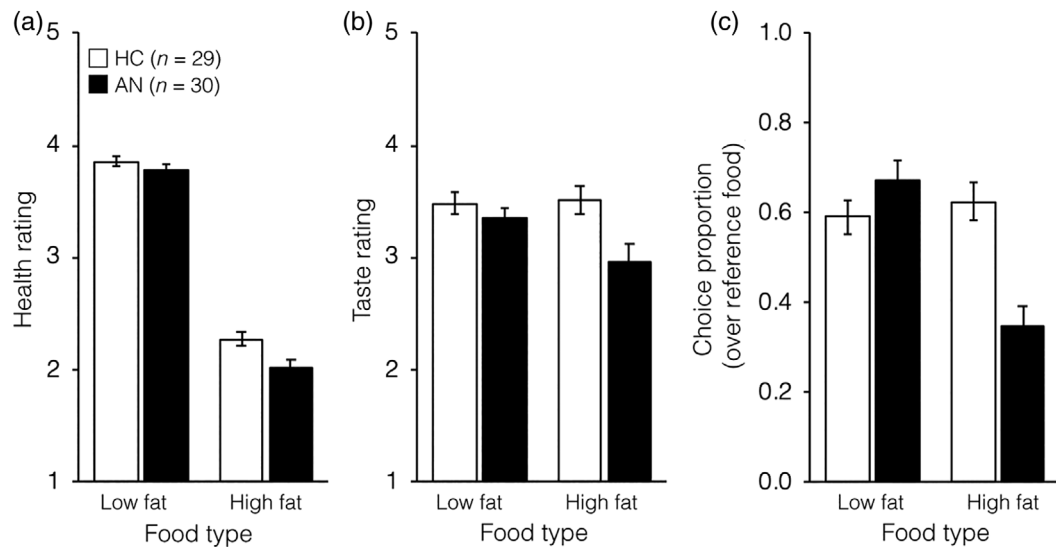


FIGURE 2 Food Choice Task behavior in individuals with anorexia nervosa and healthy control participants in the baseline research assessment. (A) Health ratings were significantly higher for low-fat foods than high-fat foods, and the anorexia nervosa group-rated foods as less healthy overall. (B) The anorexia nervosa group rated high-fat foods in particular as less tasty than did the healthy control group. (C) In the Choice phase, the anorexia nervosa group was less likely than the healthy control group to choose high-fat foods in particular. See text for description of statistically significant effects. AN, anorexia nervosa; HC, healthy control

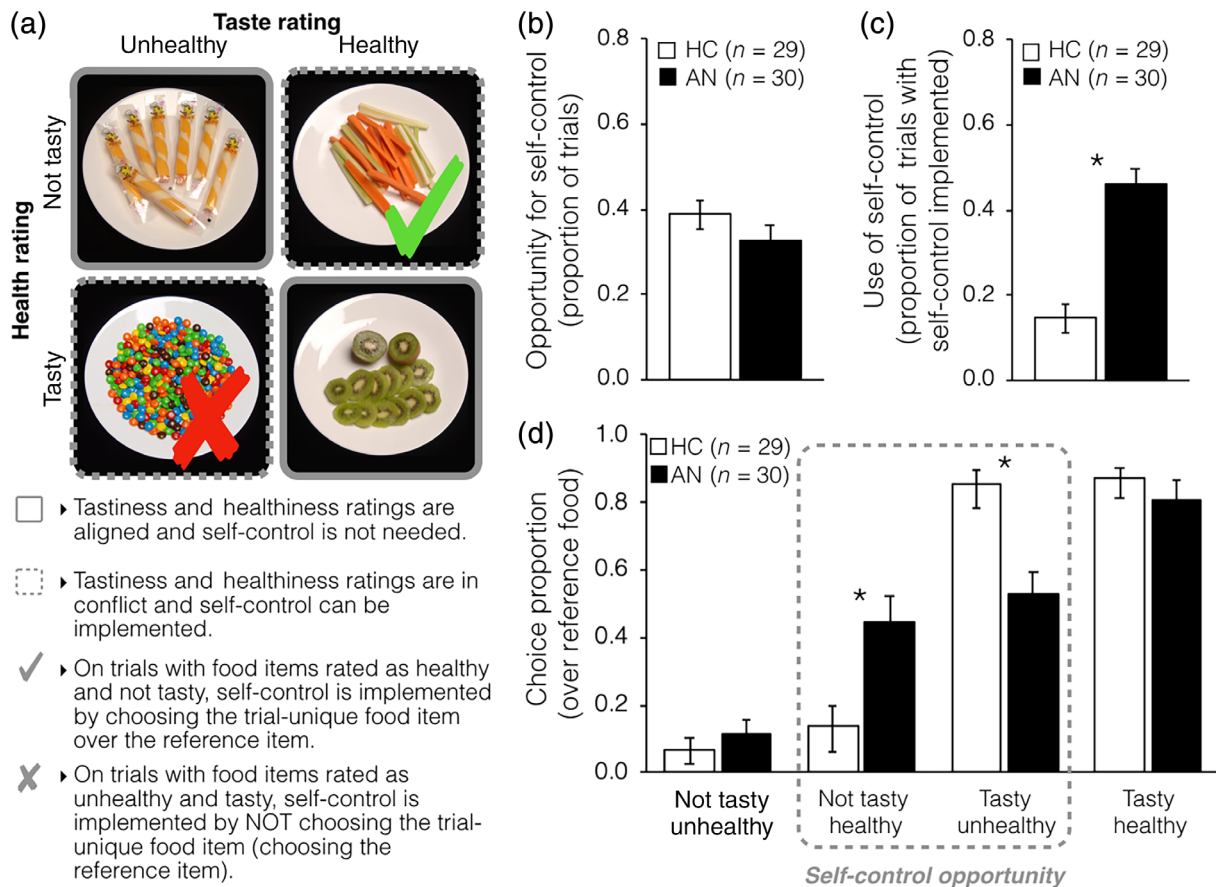


FIGURE 3 Food choices and self-control. (A) Schematic of how food ratings are used to determine trials that present opportunities to implement self-controlled choices versus trials that do not present self-control conflict. (B) The healthy control and anorexia nervosa groups had a similar proportion of trials on which self-control conflict could arise. (C) On trials presenting opportunity for self-control, the anorexia nervosa group was more likely to make self-controlled choices. (D) Self-control opportunities occurred on two different types of trials: when food items were rated as tasty and unhealthy or not tasty and healthy. The anorexia nervosa group made more self-controlled choices on both types of trials. *Indicates $p < .05$. AN, anorexia nervosa; HC, healthy control [Color figure can be viewed at wileyonlinelibrary.com]

reference item was chosen) or if a non-tasty healthy item was chosen. Self-control opportunity and implementation and choices on different self-control trial types were modeled with multilevel logistic regression.

Pearson correlation was used to assess the relationship between mean Tastiness ratings, proportion of high-fat food choices, or self-control use on the Food Choice Task at baseline with clinical parameters (e.g., duration of illness and EDE-Q Global score) in the SE-AN group.

3 | RESULTS

3.1 | Cross-sectional comparison of baseline assessment

At baseline, data were lost from four SE-AN participants and one HC due to computer error. Therefore, 30 participants with SE-AN and 29 HCs completed the task at the baseline assessment. Demographics and clinical characteristics for both groups are shown in Table 1. The groups did not differ in age ($p = .115$), but as expected, SE-AN participants had lower BMI and higher EDE-Q Global scores than HCs ($p < .001$).

TABLE 2 Demographic and clinical characteristics for anorexia nervosa participants in each arm of the rTMS trial at the baseline, post-treatment, and follow-up assessments, with the estimated between-group effect sizes (Cohen's d with 95% confidence intervals) for post-treatment and follow-up clinical characteristics (adjusted for baseline*)

	Real rTMS ($n = 13$)	Sham rTMS ($n = 13$)	t	df	p	d (95% CI)
Age (years) (mean \pm SD)	30.20 \pm 10.00	31.30 \pm 12.50	−0.24	24	.81	
Illness duration (years) (mean \pm SD)	15.96 \pm 11.40	15.40 \pm 12.20	0.13	24	.90	
AN-R/AN-BP (n)	9/4	9/4				
Treatment at baseline (n) ^a						
ED day-patient treatment	0	1				
ED outpatient treatment	10	9				
No treatment	3	4				
Antidepressant medication ^b	8	7				
Other psychotropic medication ^{b,c}	2	4				
BMI (kg/m ²) (mean \pm SD)						
Baseline	15.70 \pm 1.40	16.30 \pm 1.20	−0.97	24	.34	
Post-treatment	15.60 \pm 1.30	16.20 \pm 1.30	−1.10	24	.30	−0.16 (−0.93 to 0.61)
Follow-up	15.70 \pm 1.70	16.10 \pm 1.60	−0.70	24	.51	0.08 (−0.69 to 0.84)
EDE-Q Global (mean \pm SD)						
Baseline	4.00 \pm 1.30	4.20 \pm 0.80	−0.47	24	.64	
Post-treatment	3.70 \pm 1.20	3.80 \pm 1.30	−0.05	24	.96	0.21 (−0.56 to 0.98)
Follow-up	3.60 \pm 1.40	3.60 \pm 1.30	−0.03	24	.98	0.20 (−0.57 to 0.97)
DASS-21 Depression (mean \pm SD)						
Baseline	27.10 \pm 9.50	24.60 \pm 9.98	0.65	24	.53	
Post-treatment	22.00 \pm 10.80	21.50 \pm 9.10	0.10	24	.92	−0.20 (−0.97 to 0.58)
Follow-up	17.20 \pm 10.20	22.90 \pm 13.20	−1.10	24	.23	−0.81 (−1.61 to −0.004)
DASS-21 Anxiety (mean \pm SD)						
Baseline	16.60 \pm 8.50	14.60 \pm 12.60	0.47	24	.64	
Post-treatment	9.10 \pm 10.30	10.50 \pm 9.10	−0.36	24	.72	−0.55 (−1.33 to 0.24)
Follow-up	10.90 \pm 9.40	13.50 \pm 12.30	−0.61	24	.55	−0.69 (−1.48 to 0.11)

*Post-treatment/follow-up scores minus baseline scores. Bold font signifies that the CI do not include 0.

Abbreviations: AN-BP, anorexia nervosa binge-eating/purging type; AN-R, anorexia nervosa restricting type; BMI, body mass index; CI, confidence interval; df , degrees of freedom; DASS-21, Depression Anxiety and Stress Scales—Version 21; ED, eating disorder; EDE-Q, Eating Disorder Examination Questionnaire; SD, standard deviation.

^aReported at screening/baseline assessment.

^bMedication remained at a stable dose for the duration of rTMS treatment.

^cIncluding antipsychotics, benzodiazepine/other anxiolytic/sedative medication.

3.1.1 | Healthiness and Tastiness ratings

Figure 2 shows the average Healthiness (A) and Tastiness (B) ratings for low- and high-fat foods for the SE-AN and HC groups. Both groups rated high-fat foods as less healthy than low-fat foods ($\chi^2 = 1,176.83$, $p < .001$). Additionally, the SE-AN group rated food items as less healthy overall ($\chi^2 = 5.07$, $p = .024$). There was no interaction between Group and Food Type (high-fat vs. low-fat) on Healthiness ratings ($\chi^2 = 2.95$, $p = .086$).

For the Tastiness ratings, there was no main effect of Food Type ($\chi^2 = 3.22$, $p = .073$). There was a main effect of Group ($\chi^2 = 6.27$, $p = .012$) and a significant Group \times Food Type interaction ($\chi^2 = 4.04$, $p = .044$), indicating that the SE-AN group rated high-fat foods in particular as less tasty than did the HC group.

3.1.2 | Food choices by fat content

Figure 2C shows choice proportions for low- and high-fat foods for the SE-AN and HC groups. There was a significant main effect of Food Type ($z = -4.39$, $p < .001$), such that high-fat foods were less likely to be chosen relative to low-fat foods. There was a trend toward a main effect of Group ($z = -1.94$, $p = .0525$). We found a significant Group \times Food type interaction ($z = -5.39$, $p < .001$), demonstrating that the SE-AN group were less likely to choose high-fat foods relative to HC participants.

3.1.3 | Food choices and self-control

There was no significant group difference in the number of trials with an opportunity for self-control (proportion of trials with conflict between Healthiness and Tastiness ratings; $z = -1.14$, $p = .26$; Figure 3B). On trials that presented opportunities to make a self-controlled choice, the SE-AN group were more likely to use self-control than the HCs ($z = 5.55$, $p < .001$; Figure 2C).

When self-control use trials were considered separately (Not-Tasty Healthy choice vs. Tasty-Unhealthy choice), there was a main effect of Group for both trial types, such that SE-AN participants chose healthy, less tasty foods more ($z = 3.49$, $p < .001$) and unhealthy, tasty foods less ($z = -4.76$, $p < .001$), compared to HCs (Figure 3D).

3.1.4 | Associations between food choice and clinical parameters

Among individuals with SE-AN, there was a significant inverse correlation between mean Tastiness rating and illness duration ($r = -.47$, $p = .008$). Illness duration and age are generally tightly related, as they were in this group of participants ($r = .91$), and the correlation between illness duration and Tastiness rating did not remain significant when age was included. However, Tastiness rating and age were not correlated in the HC group ($r = -.11$, $p = .58$). In the SE-AN participants, high-fat food

choice proportion was not significantly correlated with illness duration ($r = -.31$, $p = .095$) nor EDE-Q Global Score ($r = -.18$, $p = .33$). No clinical parameters were associated with self-control use ($p > .05$).

3.2 | Effect of rTMS on food choice

Data were available for 26 (out of 30) participants who completed the trial: 13 participants who received real rTMS ($n = 13$ at baseline, $n = 12$ at post-treatment, $n = 13$ at follow-up) and 13 participants who received sham rTMS ($n = 13$ at baseline, $n = 13$ at post-treatment, $n = 12$ at follow-up). Groups did not significantly differ in baseline demographics nor in clinical characteristics (BMI, ED symptoms, depression and anxiety symptoms) at baseline, post-treatment, or follow-up assessments (Table 2). Between-group effect sizes were small for BMI and ED symptoms and moderate for anxiety symptoms at both post-treatment and follow-up (adjusted for baseline), favoring real rTMS treatment (except for BMI at post-treatment; see Table 2). Group differences for depression were of small effect at post-treatment, but of large effect ($d = -.81$, see Table 2) at follow-up, favoring real rTMS.

3.2.1 | Healthiness and Tastiness ratings

There was no significant effect of Time or rTMS Treatment Type on Healthiness or Tastiness ratings.

3.2.2 | Food choices by fat content

Similarly, there were no significant changes in food choices by fat content over time or with rTMS treatment. However, there appeared to

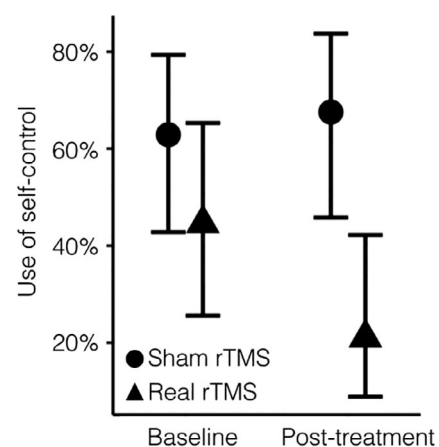


FIGURE 4 Effect of repetitive transcranial magnetic stimulation on self-control (as described in Figure 3A): the percentage of trials on which self-control was used, out of trials on which there was a conflict between Healthiness and Tastiness ratings, across sham and real rTMS groups at baseline and post-treatment. Plotted are group averages with 95% confidence intervals. rTMS, repetitive transcranial magnetic stimulation

be a trend toward an interaction between Treatment and Time for baseline versus post-treatment ($z = 1.65$, $p = .099$), such that there was a general shift in choices for both high- and low-fat foods.

3.2.3 | Food choices and self-control

Opportunities for use of self-control did not differ between sham and real rTMS groups or between time points. Comparing sham and real rTMS groups at post-treatment versus baseline, a significant effect of Treatment ($z = 2.42$, $p = .016$) was qualified by a significant interaction between Treatment and Time on the use of self-control ($z = 2.24$, $p = .025$), such that participants who received real rTMS had decreased self-control use at post-treatment, relative to baseline (Figure 4). At follow-up, an effect of Treatment was observed ($z = 2.17$, $p = .030$) that did not interact with Time ($z = 0.25$, $p = .80$).

When we examined the self-control trial types separately (Not-Tasty Healthy choice and Tasty-Unhealthy choice; see Figure 3A), there was no Treatment or Time main effects or interaction with respect to the Not-Tasty Healthy choice. However, we did find a Treatment main effect for the Tasty-Unhealthy choice ($z = -2.07$, $p = .038$) and a significant interaction between Time and Treatment ($z = -2.62$, $p = .009$), such that there was an increased selection of Tasty-Unhealthy foods in participants who received real rTMS at post-treatment (relative to baseline).

4 | DISCUSSION

In this study, we assessed the effects of 20 sessions of real or sham high-frequency (excitatory) rTMS treatment to the left DLPFC on outcomes of the Food Choice Task in people with SE-AN. As part of this, we investigated the use of the Food Choice Task in a UK-based sample to compare our data with published work (Foerde et al., 2015; Steinglass et al., 2015). Our baseline data were consistent with previous research: relative to HCs, SE-AN participants (a) rated food items as less healthy; (b) rated food items, high-fat foods in particular, as less tasty; (c) showed a preference for low-fat foods and made fewer choices of high-fat foods; and (d) exercised self-control on a greater proportion of trials (i.e., they selected Not-Tasty Healthy foods more and Tasty Unhealthy foods less). This pattern of food choice is in accord with the broader literature on dietary patterns in AN (Allen et al., 2013; Baskaran et al., 2017; Mayer et al., 2012).

rTMS treatment did not affect ratings associated with healthiness or tastiness, nor food choices by fat content in patients with SE-AN. Although not significant ($p = .099$), there was a general shift in choices away from the neutral reference food toward the trial-unique food items (both high- and low-fat) in the real rTMS group. This may reflect the development of a more flexible attitude toward food. Real rTMS (compared to sham rTMS) was also associated with significantly fewer self-controlled food choices at post-treatment, relative to baseline. This finding may have been driven by the increased choice of "Tasty-Unhealthy" foods, as the selection of "Not-Tasty Healthy" foods did

not change. A previous case series in SE-AN reported that the therapeutic effects of rTMS treatment on psychopathology (improvements in ED and affective symptoms) persisted at a 6-month follow-up (McClelland et al., 2016). Therefore, a reduction in self-controlled choices in the Food Choice Task at follow-up may have been expected. It is unclear why, in the present study, we did not observe a maintained effect on food choice at follow-up. It may be due to variability in the nature of support and treatment experiences of participants in the follow-up phase, for example, reducing or minimal/absent therapeutic support, against a background of severe and enduring illness. It is possible that combining rTMS with a form of psychological therapy or behavioral intervention might help translate the reduced self-controlled food choices into real-life long-term changes in food intake.

As the DLPFC is involved in cognitive control (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004) and AN is often characterized as a disorder of excessive self-control (Fairburn et al., 1999), it is perhaps counterintuitive that modulating this area with high-frequency (i.e., excitatory) rTMS appears to promote a more flexible approach to food choice i.e., a reduction in self-controlled choices. High-frequency rTMS to the DLPFC may have increased the cognitive control needed to override maladaptive restrictive food choices. Some possible mechanisms are discussed in the following.

Habit and reward are associated with fronto-striatal circuitry and have been implicated in the pathogenesis of AN (O'Hara et al., 2016), and more specifically, restrictive food intake (Compan et al., 2015; O'Hara, Campbell, & Schmidt, 2015; Steinglass & Walsh, 2016). For example, restrictive food intake may occur in AN because secondary (contextual) rewards, such as dietary restriction, are more rewarding than primary (immediate) rewards, such as food (Keating, 2010; Keating, Tilbrook, Rossell, Enticott, & Fitzgerald, 2012). It is also possible that, over time, restrictive food intake in AN may become a habit (Godier & Park, 2014; O'Hara et al., 2016; Steinglass & Walsh, 2016; Walsh, 2013). Thus, rTMS may increase the cognitive control needed to (a) choose rewards that carry low value but are in line with the goal of recovery or (b) disrupt maladaptive habitual behaviors. Both can be reflected in the increased proportion in choices of tastier but less healthy foods. These changes may occur via rTMS effects on neuroplasticity in the DLPFC and related neurocircuits (Cheeran, Koch, Stagg, Baig, & Teo, 2010; Houdayer et al., 2008; Zhao, Li, Tian, Zhu, & Zhao, 2019), such as those implicated in models of AN which propose etiological roles for habit and reward (Compan et al., 2015; Dunlop et al., 2016; Frank et al., 2019). For example, excitatory rTMS may alter the efficiency of the regulatory effect of the DLPFC on tonic amygdala activity, a brain region that has been associated with anxiety and the wider negative valence system (Dunlop et al., 2016).

It is also important to consider that changes in mood might be relevant to the mechanism of action of rTMS in SE-AN, as, for example, it has been proposed that in AN, dietary restriction may be used to modulate/regulate mood (Haynos & Fruzzetti, 2011). On this basis, it would be expected that rTMS-related improvements in mood would reduce the need to restrict food intake and make self-controlled choices on the Food Choice Task. However, we did not see

significantly greater improvements in mood in the real rTMS group, compared to the sham group, at post-treatment, that is, these were not evident until the follow-up (4-months post-randomization; see Table 2 and Dalton, Bartholdy, McClelland, et al., 2018). The observed reduction in self-controlled food choices associated with real rTMS was also not reflected in other measures used to assess participants' rTMS treatment response (as reported in Dalton, Bartholdy, McClelland, et al., 2018). For example, the real and sham rTMS groups did not significantly differ in weight gain, ED symptoms, anxiety, nor food-related anxiety (measured by the Fear of Food Measure, Levinson & Byrne, 2015; see Dalton, Bartholdy, McClelland, et al., 2018) at post-treatment and follow-up assessments. Given that there was not a significantly greater improvement in these clinical characteristics in the real rTMS group compared to the sham rTMS group at the post-treatment assessment, the observed reduction in self-control use in the real rTMS group is likely not attributable to clinical improvements.

4.1 | Strengths and limitations

This is the first study to systematically assess food choice before and after multiple sessions of rTMS treatment in patients with SE-AN. We used a validated Food Choice Task that allows for choices to be calibrated to individualized food preferences. The findings shed some light on potential mechanisms of action of rTMS in SE-AN. The AN sample was small and heterogenous, particularly in relation to illness duration. With increased illness duration, maladaptive behaviors may become entrenched and hence, may influence responsivity to rTMS. Also, the sample was not ethnically diverse and did not include men. Psychiatric comorbidities in the SE-AN patients were not assessed using expert-rated diagnostic interviews; however, related symptoms were measured using self-report questionnaires. Task administration was not standardized in relation to mealtimes and a few US food items were unknown to participants. The follow-up period may have been too short to identify improvements in food choice, particularly given the enduring nature of illness in our sample. However, research of real-world food intake behavior suggests that maladaptive food choices (e.g., a reduced percent of calories from fat compared to HCs) persist throughout recovery from AN (Mayer et al., 2012). Finally, we did not assess whether rTMS led to changes in everyday food intake. Despite this, our findings suggest a possible mechanism by which rTMS in SE-AN may influence illness-related behaviors, such as restrictive food intake.

5 | CONCLUSION

We assessed food choice as an outcome following 20 sessions of real or sham high-frequency rTMS treatment to the left DLPFC in patients with SE-AN. In parallel, we confirmed the results of previous Food Choice Task studies in a UK-based sample of people with SE-AN. rTMS did not alter ratings of Healthiness and Tastiness nor did it change food choices by fat content. However, real rTMS may have contributed to reduced self-control use in the Food Choice Task at post-treatment

(relative to baseline). This may be associated with neuroplastic changes in the DLPFC and associated neurocircuits. This study contributes to the emerging evidence for rTMS as a treatment for AN and to the growing literature investigating how rTMS exerts its effects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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